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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/00, 9/20

A1

(11) International Publication Number: WO 92/17161

(43) International Publication Date: 15 October 1992 (15.10.92)

(21) International Application Number: PCT/US92/01982

(22) International Filing Date: 13 March 1992 (13.03.92)

(30) Priority data:
680,498 4 April 1991 (04.04.91) US

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CHEWABLE ANTACID COMPOSITIONS

(57) Abstract

Compressed pharmaceutical compositions in unit dosage forms suitable for ingestion by chewing (such as chewable antacid tablets) comprise a pre-granulated antacid agent and granulated mannitol, wherein these ingredients are dry blended and direct compressed into a unit dosage form.

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CHEWABLE ANTACID COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates to compressed pharmaceutical compositions in unit dosage forms suitable for ingestion by chewing, said compositions comprising a pre-granulated antacid agent and granulated mannitol, wherein these ingredients are dry blended and direct compressed into a unit dosage form.

Pharmaceutical compositions containing antacid agents useful for treating gastrointestinal disorders are widely used. They vary in the active ingredients, and increasingly differ in the flavors, texture and even forms.

In spite of the large amount of research directed to developing chewable antacid compositions, commercial products to date continue to fail to meet consumer's expectation for an aesthetically acceptable product. Especially undesirable for the commercial products is the gritty and/or chalky texture and taste/aftertaste present to varying degrees in current products. There continues, therefore, to be a need for antacid products in unit dosage forms suitable for chewing for ingestion which have improved aesthetics. It has been surprisingly discovered that chewable antacid compositions having improved aesthetics can be prepared by a simple, direct compression method of a granulate dry blend when the dry blend comprises granulate mannitol and a pre-granulated antacid agent.

Thus, an object of the present invention is to provide chewable antacid compositions having improved aesthetics. A further object is to provide unit dosage form antacid compositions suitable for ingestion by chewing which have improved texture (e.g., reduce grittiness and/or chalkiness), improve taste and aftertaste, quick disintegration properties, and/or rapid clearance from the mouth, as well as other attributes desirable of a chewable antacid composition. A further object is to provide a simple and efficent process for manufacturing chewable antacid compositions having improved aesthetics, wherein such process

involves direct compression of a dry blend of granulate mannitol and pre-granulated antacid agent.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements are made at 25°C, unless otherwise specified.

SUMMARY OF THE INVENTION

The present invention is directed to compressed compositions in unit dosage form suitable for ingestion by chewing comprising: (a) pre-granulated antacid agents; and (b) granulated mannitol, and wherein further said compositions are prepared by dry blending these ingredients and direct compressing the blend to a unit dose form.

The present invention also relates to a process for making compressed compositions in unit dosage forms suitable for ingestion by chewing. Said process comprises the steps of: (a) dry blending a composition comprising pre-granulated antacid agent and granulated mannitol; and (b) direct compressing the resulting blend into unit dosage forms suitable for ingestion by chewing.

DETAILED DESCRIPTION OF THE INVENTION

The present invention compositions comprise a pre-granulated antacid agent as described hereinafter and granulate mannitol compressed into a unit dose form suitable for ingestion by chewing.

Granulate mannitol useful in the compositions of the present invention is commercially available. It is sold, for example, by ICI Americas, Inc., Wilmington, Delaware. Granulate mannitol preferably has a particle size of less than about 1.8mm. Typically, compositions of the present invention comprise from about 25% to about 75% granulate mannitol, preferably from about 30% to about 70%, and most preferably from about 40% to about 60% by weight of the compressed unit dose form.

The term "pre-granulated antacid agent" as used herein, means antacid agents which have been granulated with gelatin and/or simple sugars (e.g., glucose and/or dextrose). The term "antacid agents", as used herein, means not only those ingestible pharmaceutical actives generally recognized as providing benefits

by neutralizing stomach acid, but also other ingestible pharmaceutical agents effective for treating the gastrointestinal tract, such as bismuth-containing agents and H_2 receptor-blocking anti-secretory agents, which are preceived as having negative aesthetics improved by compositions according to the present invention. Preferred are antacid agents which have stomach acid neutralizing capacities, such as those agents selected from the group consisting of: aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, and mixtures thereof. Bismuth-containing agents include, for example, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, and mixtures thereof. A particularly preferred bismuth salt is bismuth subsalicylate. Examples of H_2 receptor-blocking anti-secretory agents include ranitidine and cimetidine. Preferred antacid agents for use herein are aluminum hydroxide, magnesium hydroxide, dihydroxy aluminum sodium carbonate, calcium carbonate, and mixtures thereof. Most preferred is calcium carbonate.

Pre-granulated antacid agents are commercially available, being sold for example by Wittaker Clark & Daniels, Philadelphia, Pennsylvania. Preferred pre-granulated antacid agents comprise more than about 50%, preferably more than about 75%, and most preferably about 90% or more of antacid agent by weight of the pre-granulate. Also, preferred pre-granulated antacid agents comprise less than about 50% of a granulating agent selected from gelatin, simple sugars, and mixtures thereof; preferably less than about 25%, and more preferably about 10% or less of these granulating agents by weight of the pre-granulate. The term "simple sugars", as used herein, means monosaccharides, disaccharides, and such similar low molecular weight saccharide

materials which are safe and effective for ingestion by a human and which are effective for granulated antacid agents when used alone or with gelatin. Most preferred is pre-granulated calcium carbonate comprising from about 80% to about 95% and preferably from about 90% to about 95% calcium carbonate, from about 0.1% to about 5% and preferably from about 0.1% to about 1% gelatin, and from about 1% to about 20% and preferably from about 1% to about 9% glucose. Such pre-granulate is again commercially available from Wittaker Clark & Daniels, Philadelphia, PA.

Typically, the compositions of the present invention comprise from about 25% to about 75% pre-granulated antacid agent by weight of the pharmaceutical composition, preferably from about 30% to about 70%, and most preferably from about 35% to about 50%.

The compositions of the present invention also preferably comprise excipients suitable for use in the present unit dose forms suitable for ingestion by chewing. The term "excipients", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for oral administration to a human. The term "compatible", as used herein, means that the components of the compositions of the present invention are capable of being commingled with the antacid active, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compositions under ordinary use situations. Excipients must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human being treated.

Preferred pharmaceutical compositions of the present invention also comprise as part or all of the excipients an amount of 3-l-menthoxy propane 1,2-diol ("MPD") effective for providing a cooling sensation to the throat. This material is described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et al., incorporated herein by reference in its entirety. MPD is commercially available from Takasago Perfumery Co., Ltd., Tokyo, Japan.

Some examples of other substances which can serve as excipients are sugars such as lactose, glucose and sucrose;

starches such as cornstarch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; and alginic acid; as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, sweetening agents (including non-nutritive sweeteners such as aspartame and saccharin), cooling agents, tableting agents, stabilizers, antioxidants, and preservatives, can also be present. Other compatible pharmaceutical additives and actives (e.g., NSAI drugs; pain killers; muscle relaxants) may be included in the compositions of the present invention. Also, it is to be noted that in addition to the MPD, other materials having cooling properties may also optionally be included within the excipients, such as menthol, and N-ethyl-p-menthane-3-carboxamide ("WS-3", supplied by Sterling Drugs).

The choice of excipients to be used in conjunction with the pharmaceutical active of the present compositions is basically determined by the dose form for the compositions. The preferred dosage forms are compressed chewable tablets comprising a safe and effective amount of the antacid agent. Excipients suitable for the preparation of such unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art.

The excipients employed in the present compositions are used at concentrations sufficient to provide a practical size to dosage relationship. Typically, excipients comprise from about 1% to about 50% by weight of the pharmaceutical compositions of the present invention, preferably from about 1% to about 40%, and most preferably from about 1% to about 25%. Additionally, the MPD

preferably comprises from about 0.01% to about 0.50% by weight of the pharmaceutical compositions of the present invention, preferably from about 0.02% to about 0.20%, and most preferably from about 0.04% to about 0.10%.

The process for making compositions of the present invention comprised of steps: (a) dry blending a composition comprising pre-granulated antacid agent and granulate mannitol; and (b) direct compressing the resultant blend into unit dosage forms suitable for ingestion by chewing. Preferably, the optional excipients are dry blended with the composition during step (a), but some or all of the excipients may be added as part of the pre-granulated antacid and/or granulated mannitol, or may be added after compression of the composition such as by coating the compressed unit dosage form. Preferred dosage forms are compressed to a hardness of at least about 6 Strong Cobb Units ("S.C."), preferably within from about 6 S.C. to about 15 S.C.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as a limitation of the present invention as many variations thereof are possible without departing from the spirit and scope.

Example I

An ingestible pharmaceutical composition according to the present invention in the form of a chewable antacid tablet is prepared as follows:

Ingredients	Weight %
Granulated calcium carbonate[1)]	42.87%
Magnesium stearate	2.50%
Colored speckles	0.75%
Flavorants	0.78%
MPD[2)]	0.07%
WS-3[3)]	0.05%
Aspartame	0.198%
Sodium Saccharin	0.102%
Mannitol[4)]	Q.S.

1) Granulated calcium carbonate containing 93.3% calcium carbonate, 6.3% glucose and 0.4% gelatin; supplied by Whittaker Clark & Daniels, Philadelphia, Pa.
2) 3-l-menthoxy propane 1,2-diol, supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan.
3) N-ethyl-p-menthane-3-carboxamide, supplied by Sterling Drugs.
4) Granulate mannitol supplied by ICI Americas, Inc., Wilmington, Delaware.

The above ingredients are dry blended in a mixer until homogeneous, and then direct compressed in a tabletting machine to approximately 8.5 S.C. hardness to produce chewable antacid tablets each weighing 1.25g (500mg calcium carbonate per tablet).

Ingestion of one or two of these tablets by a human subject suffering from heartburn, acid indigestion, and upset stomach associated with these symptoms provides effective relief for this upper gastrointestinal tract distress.

WHAT IS CLAIMED IS:

1. Compressed compositions in unit dosage form suitable for ingestion by chewing comprising:
(a) pre-granulated antacid agent; and
(b) granulated mannitol;
and wherein further said compositions are prepared by dry blending the pre-granulated antacid agent and the granulated mannitol and direct compressing this blend in to a unit dose form.

2. Compressed compositions according to Claim 1 wherein the antacid agent present in the pre-granulated antacid agent is selected from the group consisting of antacid agents which have stomach acid neutralizing capacities, bismuth-containing agents, H_2 receptor-blocking anti-secretory agents, and mixtures thereof.

3. Compressed compositions according to either of Claims 1 or 2 wherein the antacid agent is selected from the group consisting of aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, ranitidine, cimetidine, and mixtures thereof.

4. Compressed compositions according to any of Claims 1-3 wherein the pre-granulated antacid agent is granulated with gelatin and at least one simple sugar.

5. Compressed compositions according to Claim 4 wherein the simple sugar is selected from the group consisting of glucose, dextrose, and mixtures thereof.

6. Compressed compositions in unit dosage form suitable for ingestion by chewing comprising:
(a) from 25% to 75% pre-granulated antacid agent comprising at least one antacid agent selected from the group consisting of aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, and mixtures thereof, and wherein further said pre-granulated antacid agent is granulated with gelatin and at least one simple sugar; and
(b) from 25% to 75% granulated mannitol;
and wherein further said compositions are prepared by dry blending the pre-granulated antacid agent and the granulated mannitol and direct compressing this blend to a unit dose form.

7. Compressed compositions according to Claim 6 wherein the antacid agent is calcium carbonate and the simple sugar is selected from the group consisting of glucose, dextrose, and mixtures thereof.

8. Compressed chewable antacid tablets comprising:
(a) from 35% to 50% pre-granulated antacid agent comprising from 80% to 95% calcium carbonate, from 0.1% to 5% gelatin, and from 1% to 20% glucose;
(b) from 40% to 60% granulated mannitol; and

(c) from 1% to 25% excipient selected from the group consisting of wetting agents, lubricants, flavoring agent, tableting agents, stabilizers, antioxidants, preservatives, sweetening agents, cooling agents, and mixtures thereof;

and wherein further said compressed tablets are prepared by dry blending the pre-granulated antacid agent and the granulated mannitol and direct compressing this blend to a tablet unit dose form.

9. Compressed chewable antacid tablet compositions according to any of Claims 1-8 comprising from 0.01% to 0.50% 3-l-menthoxy propane 1-2-diol.

10. A process for making a compressed composition according to any of Claims 1-9 comprising the steps of:

(a) dry blending a composition comprising pre-granulated antacid agent and granulated mannitol; and

(b) direct compressing the resulting blend into a unit dosage form suitable for ingestion by chewing.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01982

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/00 A 61 K 9/20

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	EP,A,0396335 (BEECHAM) 7 November 1990, see claims 1,4,14-16; page 2, lines 42-43; page 3, lines 27-28,45-47 ---	1-10
Y	EP,A,0338861 (WALTON) 25 October 1989, see claims 1-2,7-10; column 4, examples 1,2; column 5, example 3 ---	1-10
Y	US,A,4446135 (H.A. FOUNTAINE) 1 May 1984, see claims 1-4; column 3, lines 1-45; column 4, lines 1-5 ---	1-10
Y	US,A,4327077 (W.J. PUGLIA) 27 April 1982, see claims 1,4-5,8,10-11; column 3, lines 42-55; column 4, lines 45-60 --- -/-	1-10

* Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05-08-1992	04. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (C NTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	US,A,4163777 (A.K. MITRA) 7 August 1979, see claims; column 2, lines 35-52; column 3, lines 8-38; column 4, example 1; column 8, example 7	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201982 SA 59070

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/08/92
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		JP-A-	2295919	06-12-90
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